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The Patent Office
Cardiff Road
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1. Your reference — MG/PMS/PB60227P1

2. Patent application number *(The Patent Office will fill in his part)* — 0 2 OCT 2003 | 0323109.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   Glaxo Group Limited
   Glaxo Wellcome House, Berkeley Avenue,
   Greenford, Middlesex UB6 0NN, Great Britain

   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom 4735872003

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   GlaxoSmithKline
   Corporate Intellectual Property (CN9 25.1)
   980 Great West Road
   BRENTFORD
   Middlesex TW8 9GS

   Patents ADP number *(if you know it)* 7960982003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is named as an applicant, or
   c) any named applicant is a corporate body
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Patents Form 1/77

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Continuation sheets of this form	0
Description	34
Claim(s)	2
Abstract	0
Drawings	0

10. If you are also filing any of the following, state how many against each item.

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Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patents Form 9/77)*

Request for substantive examination *(Patents Form 10/77)*

Any other documents *(please specify)*

11. We request the grant of a patent on the basis of this application

Signature _____ Date 2-Oct-03

M Gibson

12. Name and daytime telephone number of person to contact in the United Kingdom

M Gibson 01279 644841

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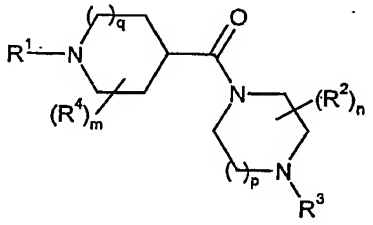
NOVEL COMPOUNDS

The present invention relates to novel piperidine carbonyl piperazine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

WO 97/06802 (Zeneca Limited) describe a series of pyridyl and pyrimidyl derivatives as oxido-squalene cyclase inhibitors which are claimed to lower blood cholesterol. WO 02/76925 (Eli Lilly), WO 03/004480, WO 03/024928 and WO 03/024929 (all Novo Nordisk A/S and Boehringer Ingelheim International) describe a series of substituted piperidines or piperazines which are claimed to bind selectively to the histamine H3 receptor.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:
R^1 represents aryl, heteroaryl, -aryl-X-C_{3-7} cycloalkyl, -heteroaryl-X-C_{3-7} cycloalkyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-heteroaryl, -heteroaryl-X-aryl or –heteroaryl-X-heterocyclyl;
wherein said aryl, heteroaryl and heterocyclyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, -COC_{1-6} alkyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$C(R^{15})$=NOR^{16}, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;
X represents a bond, O, CO, SO_2, OCH_2 or CH_2O;
each R^2 and R^4 independently represents C_{1-4} alkyl;
R^3 represents C_{3-8} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl or -C_{1-4}alkyl-C_{3-6} cycloalkyl;
wherein said C_{3-6} cycloalkyl groups of R^3 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, C_{1-4} alkyl or trifluoromethyl groups;
m and n independently represent 0, 1 or 2;
p and q independently represent 1 or 2;
or a pharmaceutically acceptable salt thereof.

Specific compounds of formula (I) which may be mentioned are those wherein R^1 represents pyridyl or pyrimidyl optionally substituted by one or two hydrogen, amino, halogen, cyano, C_{1-6} alkyl or C_{1-6} alkoxy groups and R^3 represents C_{3-8} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl or C_{5-6} cycloalkenyl.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine and the term 'polyhalo' is used herein to refer to a moiety containing more than one (eg. 2-5) of said halogen atoms.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl and tetrahydronaphthalenyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated

aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, diazepanyl and azepanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine or tetrahydroisoquinolinyl.

The term "heteroaryl" is intended to mean a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R^1 represents

aryl (eg: phenyl or naphthyl) optionally substituted by one or more (eg. 1, 2 or 3) halogen (eg. fluorine or chlorine), C_{1-6} alkyl (eg. isopropyl), polyhaloC_{1-6} alkyl (eg. CF_3), C_{1-6} alkoxy (eg. methoxy or isopropyloxy), polyhaloC_{1-6} alkoxy (eg. trifluoromethoxy or difluoromethoxy), -COC_{1-6} alkyl (eg. –COMe), -C(R^{15})=NOR^{16} (eg. –C(Me)=NOMe or –C(Me)=NOEt), cyano or C_{1-6} alkoxycarbonyl (eg. ethoxycarbonyl) groups;

heteroaryl (eg. pyridyl, pyrimidyl or benzothiazole) optionally substituted by one or more (eg. 1, 2 or 3) cyano, halogen (eg. bromine or chlorine), polyhaloC_{1-6} alkyl (eg. CF_3), C_{1-6} alkoxy (eg. methoxy) or C_{1-6} alkoxycarbonyl (eg. methoxycarbonyl) groups;

-heteroaryl-X-heteroaryl (eg. -pyrimidyl-pyridyl);

-heteroaryl-X-heterocyclyl (eg. -pyrimidyl-morpholinyl or -pyrimidinyl-dihydrobenzofuranyl);

-heteroaryl-X-aryl (eg. –pyrimidinyl-phenyl) optionally substituted by one or more (eg. 1, 2 or 3) cyano or C_{1-6} alkylsulfonyl (eg. $MeSO_2$) groups;

-aryl-X-heterocyclyl (eg. –phenyl-CO-morpholinyl) optionally substituted by one or more (eg. 1, 2 or 3) halogen groups (eg. –2-chlorophenyl-CO-morpholinyl);

-aryl-X-aryl (eg. –phenyl-O-phenyl); or

-aryl-X-C_{3-7} cycloalkyl (eg. –phenyl-CO-cyclopropyl).

More preferably, R^1 represents

aryl (eg. phenyl or naphthyl) optionally substituted by one or more (eg. 1, 2 or 3) halogen (eg. fluorine or chlorine), C_{1-6} alkyl (eg. isopropyl), polyhaloC_{1-6} alkyl (eg. CF_3),

C_{1-6} alkoxy (eg. methoxy or isopropyloxy), polyhaloC_{1-6} alkoxy (eg. trifluoromethoxy or difluoromethoxy), -C(R^{15})=NOR^{16} (eg. –C(Me)=NOMe or –C(Me)=NOEt), cyano or C_{1-6} alkoxycarbonyl (eg. ethoxycarbonyl) groups; or

heteroaryl (eg. pyridyl, pyrimidyl or benzothiazole) optionally substituted by one or more (eg. 1, 2 or 3) cyano, halogen (eg. bromine or chlorine), polyhaloC_{1-6} alkyl (eg. CF_3), C_{1-6} alkoxy (eg. methoxy) or C_{1-6} alkoxycarbonyl (eg. methoxycarbonyl) groups.

Most preferably, R^1 represents

phenyl optionally substituted by one or more (eg. 1, 2 or 3) halogen (eg. fluorine or chlorine), polyhaloC_{1-6} alkyl (eg. CF_3) or cyano groups; or

pyridyl optionally substituted by one or more (eg. 1, 2 or 3) halogen (eg. bromine or chlorine), polyhaloC_{1-6} alkyl (eg. CF_3) or cyano groups.

Preferably X represents a bond or CO, more preferably a bond.

Preferably, m represents 0.

Preferably, n represents 0 or 2, more preferably 0.

Preferably, p represents 1 or 2, more preferably 2.

Preferably, q represents 1.

When present, preferably R^2 represents methyl.

Preferably, R^3 represents C_{3-8} alkyl (eg. isopropyl, isobutyl or isopentyl) or C_{3-6} cycloalkyl (eg. cyclobutyl or cyclopentyl), more preferably isopropyl or cyclobutyl.

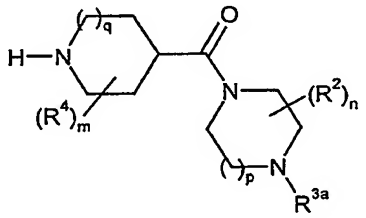
Preferred compounds according to the invention include examples E1-E69 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

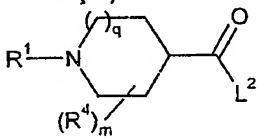
(a) reacting a compound of formula (II)



(II)

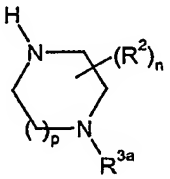
or an optionally activated or protected derivative thereof, wherein R^2, R^4, m, n, p and q are as defined above and R^{3a} is as defined for R^3 above or a group convertible to R^3, with a compound of formula R^1-L^1, wherein R^1 is as defined above and L^1 represents a suitable leaving group, such as a halogen atom (eg. fluorine, chlorine, bromine or iodine) followed by a deprotection reaction as necessary; or

(b) reacting a compound of formula (III)



(III)

wherein R^1, R^4, m and q are as defined above and L^2 represents OH or a suitable leaving group, such as a halogen atom (eg. chlorine), with a compound of formula (IV)



(IV)

wherein R^2, n and p are as defined above R^{3a} is as defined for R^3 above or a group convertible to R^3; or

(c) deprotecting a compound of formula (I) or converting groups which are protected; and optionally thereafter

(d) interconversion to other compounds of formula (I).

Process (a) typically comprises the use of a suitable base, such as potassium carbonate in a suitable solvent such as dimethylsulfoxide or N,N-dimethylformamide at elevated temperature. Alternatively process (a) may be carried out with a suitable catalyst such as bis(dibenzylideneacetone)palladium / 2-dicyclohexylphosphine-2'-(N,N-dimethylamino)-biphenyl or bis (tri-t-butylphosphine)palladium(0) in the presence of a suitable base such as sodium t-butoxide in a solvent such as o-xylene or dioxane.

An R^{3a} group convertible to R^3 may for example be a protecting group such as tert-butoxycarbonyl which may be removed under acidic conditions, eg trifluoroacetic acid or HCl to give a compound where R^3 represents hydrogen. Subsequent conversion to a compound where R^{3a} represents R^3 may be carried out by reductive amination with a compound of formula R^3=O in the presence of sodium triacetoxyborohydride or alkylation with a compound of formula R^3-L^3 where L^3 is a leaving group such as bromine or iodine.

Process (b) typically comprises activation of the compound of formula (III) wherein L^2 represents OH with a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in the presence of 1-hydroxybenzotriazole (HOBT) in a suitable solvent such as dichloromethane followed by reaction with the compound of formula (IV).

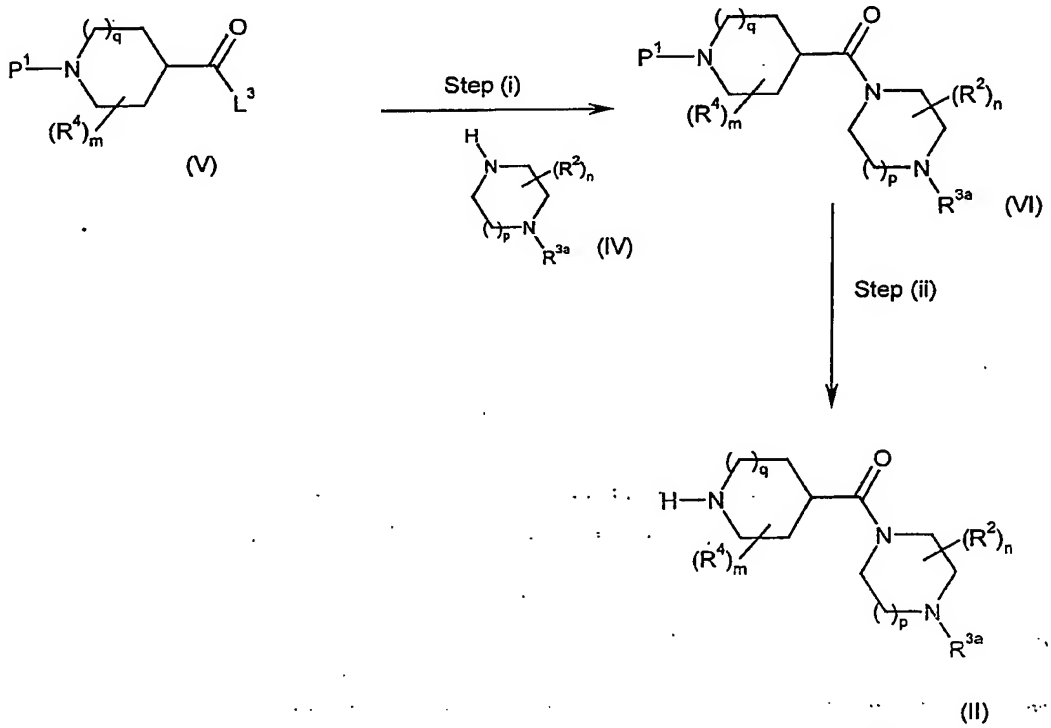
Process (b) may also involve halogenation of the compound of formula (III) wherein L^2 represents OH with a suitable halogenating agent (eg. thionyl chloride) followed by reaction with the compound of formula (IV) in the presence of a suitable base such as triethylamine or a solid supported base such as diethylaminomethylpolystyrene in a suitable solvent such as dichloromethane

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic

substitution, ester hydrolysis or amide bond formation or coupling reactions such as those involving aryl halides and amines.

Compounds of formula (II) may be prepared in accordance with the following procedure:



(V) (IV) (VI) (II)

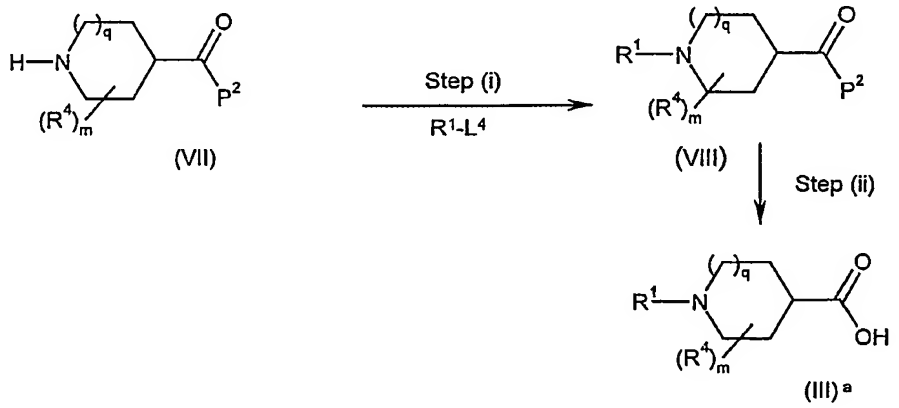
wherein R^2, R^4, m, n, p and q are as defined above, R^{3a} is as defined for R^3 above or a group convertible to R^3, L^3 represents OH or a suitable leaving group such as a halogen atom (eg. chlorine), and P^1 represents a suitable protecting group such as t-butoxycarbonyl.

When L^3 represents OH, step (i) typically comprises the use of suitable coupling conditions eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in the presence of 1-hydroxybenzotriazole (HOBT) or 1-hydroxy-7-azabenzotriazole (HOAT).

When L^3 represents a suitable leaving group such as a halogen atom (eg. chlorine), step (i) typically comprises the use of a suitable base such as triethylamine in a suitable solvent such as dichloromethane.

Step (ii) typically comprises a suitable deprotection reaction using standard conditions such as those described above for process (c). Where P^1 is a tert butoxycarbonyl group this may involve a suitable acid such as HCl or trifluoroacetic acid

Compounds of formula (III) wherein L^2 represents OH, may be prepared in accordance with the following procedure:



(VII) (VIII) (III)a

wherein R^1, R^4, m and q are as defined above, L^4 represents a suitable leaving group such as a halogen atom and P^2 represents a suitable protecting group such as methoxy, ethoxy or t-butoxy.

Step (i) is typically carried out in a suitable solvent such as N,N-dimethylformamide in the presence of a base such as potassium carbonate. Alternatively step (i) may be carried out with a suitable catalyst such as bis(dibenzylideneacetone)palladium / 2-dicyclohexylphosphine-2'-(N,N-dimethylamino)-biphenyl or bis (tri-t-butylphosphine)palladium(0) in the presence of a suitable base such as sodium t-butoxide in a solvent such as o-xylene or dioxane.

Step (ii) typically comprises a suitable deprotection reaction using standard conditions such as those described above for process (c). Where P^2 is an alkoxy group such as ethoxy this may involve a suitable acid such as HCl or a base such as sodium hydroxide.

Compounds of formula (III) wherein L^2 represents a suitable leaving group, such as a halogen atom (eg. chlorine) may be prepared by treating a compound of formula $(III)^a$ with thionyl chloride or oxalyl chloride.

Compounds of formula (IV), (V) and (VII) are either known in the literature or can be prepared by analogous methods.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, migraine,

Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT_6 antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be

frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1
1-Isopropyl-4-(piperidine-4-carbonyl)-piperazine (D1)
1-*tert*-Butoxycarbonyl-piperidine-4-carboxylate (5g) in DMF (60ml) was treated with EDC (5.5g) followed by HOAT (0.1g). After 5min, N-isopropylpiperazine (2.8g) in DMF (5ml) was added and the reaction was left stirring for 18h. The reaction was then diluted with EtOAc (150ml) and washed with saturated brine/sodium hydrogen carbonate (1:1, 200ml) followed by brine (3x200ml). The EtOAc layer was evaporated to near dryness and the residue treated with TFA/water (40ml, 95:5) for 5h prior to evaporation and re-evaporation from toluene (3x60ml). The residue was taken up into a minimum volume of EtOAc and treated with HCl (30ml, 2N solution in diethyl ether) for 1h. The resulting dihydrochloride salt was filtered off and washed with diethyl ether before drying under vacuum (4.8g). Dissolving the dihydrochloride in water and basifying with potassium carbonate, followed by extraction with EtOAc and evaporation gave the title compound (D1) as the free base (3.5g). ^{1}H NMR δ [MeOH-d4]: 1.073 (6H, d, J= 6.4Hz), 1.69-1.75 (4H, m), 2.5-2.58 (4H, m), 2.69-2.82 (3H, m), 2.85-2.94 (1H, m), 3.13-3.22 (2H, m) and 3.54-3.65 (4H, m).

Description 2
1-Isopropyl-4-[1-(5-bromo-pyrimidin-2-yl)-piperidine-4-carbonyl]-piperazine (D2)
Potassium carbonate (2.06g) was added to a mixture of 5-bromo-2-chloropyrimidine (2.89g) and 1-isopropyl-4-(piperidine-4-carbonyl)-piperazine (D1) (3.57g) in DMF (60ml). The reaction mixture was allowed to stir at rt overnight. The DMF was removed by

evaporation and the resulting residue was partitioned between H_2O/EtOAc(20:20ml). The EtOAc layer was dried ($MgSO_4$) and filtered, the filtrate was evaporated to dryness to give the title compound (D2) as a white solid (4g). ^1H NMR δ [DMSO-d6]: 0.98 (6H, d, J=6.5), 1.4-1.5 (2H, m),1.6-1.7 (2H, m), 2.30-2.35 (2H, m), 2.40-2.48 (2H, m), 2.64-2.70 (1H, m) 2.93-3.00 (3H, m), 3.4-3.55 (4H, m) 4.52-4.59 (2H,m) 8.45 (2H, s).

Description 3

1-(4-Cyanophenyl)-piperidine-4-carboxylic acid (D3)

Step 1 : Ethyl 1-(4-cyanophenyl)-piperidine-4-carboxylate

To 4-fluorobenzonitrile (11.56g) in DMSO (200ml) was added piperidine-4-carboxylic acid ethyl ester (15g) and potassium carbonate (14.4g) and the reaction was heated to 120°C for 4h. After cooling solvent was evaporated and the residue taken up into EtOAc (150ml) and washed with HCl (1M, 2x100ml), sodium hydrogen carbonate solution (2 x 100ml) and brine (100ml). Evaporation of the organic layer provided the subtitled compound (22.6g). LCMS electrospray(+ve) 259 (MH^+).

Step 2 : 1-(4-Cyanophenyl)-piperidine-4-carboxylic acid

The product of D3, Step 1 (22.6g) was dissolved in 1,4-dioxane (150ml) and 2M sodium hydroxide (87ml). The reaction was then stirred at rt for 2h and then further 2M sodium hydroxide (87ml) was added and the reaction heated to 70°C for 2h. The reaction mixture was then evaporated and the residue acidified to pH-2 with aqueous 2N HCl. The aqueous solution was then extracted with DCM (2 x 200ml) and the combined organic layers washed with brine (100ml), dried ($MgSO_4$) and evaporated to give the title compound (D3) as a white solid (14.8g). LCMS electrospray(+ve) 231 (MH^+).

Description 4

1-[1-(4-Cyanophenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (D4)

Step 1: 1-*tert*-Butoxycarbonyl- 4-[1-(4-cyanophenyl)-piperidine-4-carbonyl]-[1,4]diazepane

1-(4-Cyanophenyl)-piperidine-4-carboxylic acid (D3) (3.94g), HOBT (1.01g), TEA (2.7 ml) and 1-*tert*-butoxy-carbonyl-1,4-diazepane (3.0g) were stirred in DMF (25ml) and then EDC (3.7g) was added and the reaction stirred at rt overnight. The solvent was evaporated and the residue re-dissolved in DCM (100ml) and washed with saturated sodium hydrogen carbonate (2 x 80ml), brine (75ml) and the organic layer dried ($MgSO_4$) and evaporated. The crude product was then purified by column chromatography [silica gel, step gradient 0-10% MeOH in DCM]. Fractions containing the required product were evaporated to give the subtitled compound as a white solid (0.92g). LCMS electrospray(+ve) 413 (MH^+).

Step 2: 1-[1-(4-Cyanophenyl)-piperidine-4-carbonyl]-[1,4]diazepane hydrochloride

The product of D4, Step 1 (0.92g) was dissolved in DCM (25ml) and 4N HCl in 1,4-dioxane (5ml) was added and the reaction stirred at rt for 2h. The solvent was then evaporated to give the title compound (D4) as a white solid (0.77g). LCMS electrospray(+ve) 313 (MH^+).

Description 5

1-Cyclopentyl-4-(piperidine-4-carbonyl)-piperazine di-hydrochloride (D5)

Step 1: 1-Cyclopentyl-4-[1-*tert*-butoxycarbonyl-piperidine-4-carbonyl]-piperazine di-hydrochloride

1-*tert*-Butoxycarbonyl-piperidine-4-carboxylic acid (2.2g) in dry DMF (40ml) was treated with EDC (3.71g) followed by HOAT (0.1g). After 5min, N-cyclopentylpiperazine (1.5g) in dry DMF (5ml) was added and the reaction mixture was stirred at rt for 18h. Excess DMF was removed by evaporation and the resulting residue was re-dissolved in DCM, adsorbed onto silica gel (10g) and purified by chromatography [silica gel 0-10% MeOH (containing 10% 0.88 ammonia solution/ DCM)]. The pure fractions were combined and the solvent removed by evaporation to give the subtitled compound (2g). LCMS electrospray(+ve) 366(MH^+).

Step 2: 1-Cyclopentyl-4-(piperidine-4-carbonyl)-piperazine di-hydrochloride

The product of D5, Step 1 (2g) was dissolved in dry MeOH (30ml) and treated with 4N dioxan/HCl (5ml). The reaction mixture was stirred at rt for 18h. Excess solvent was removed by evaporation to give the title compound (D5) as a cream solid (2g). LCMS electrospray (+ve) 266(MH^+).

Description 6

1-Cyclobutyl-piperazine di-hydrochloride (D6)

Step 1: 1-tert-Butoxycarbonyl-4-cyclobutyl-piperazine

1-tert-Butoxycarbonyl-piperazine (5.6g) was dissolved in dry DCM (100ml) followed by the addition of cyclobutanone (2.10g). The reaction mixture was stirred at rt for 30min. Sodium triacetoxyborohydride (6.37g) was added portion-wise over 15min. The mixture was then stirred at rt overnight to give a black solution. The reaction mixture was washed with 1N NaOH (70ml) and the DCM layer was separated, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give the subtitled compound as an oil (6.1g) ^1H NMR δ [DMSO-d6]: 1.39 (6H, s), 1.68-1.87 (4H, m), 1.9-2.01 (2H, m), 2.15-2.2 (3H, m), 2.5 (1H, m),2.6-2.78 (1H, m), 3.18-3.3 (4H, m).

Step 2: 1-Cyclobutyl-piperazine di-hydrochloride

The product of D6, Step 1 (5.1g) was dissolved in dry MeOH (150ml) followed by the addition of 4N HCl in dioxan (10ml). The reaction mixture was stirred at rt overnight before being evaporated to dryness to give the title compound as a white solid (D6) (4g).

Description 7

1-Cyclobutyl-4-(piperidine-4-carbonyl)-piperazine di-hydrochloride (D7)

1-Cyclobutyl-piperazine di-hydrochloride (D6) (1.8g) in DMF (15ml) was stirred with sodium hydrogen carbonate (1.53g) for 5min before being added to a DMF (15ml) solution of 1-tert-butoxycarbonyl-piperidine-4-carboxylate (1.94g), EDCI (3.2g) and HOAT (0.05g). After 4h the reaction was diluted with EtOAc and washed with saturated sodium hydrogen carbonate solution and brine (3x), before being evaporated. The

residue was dissolved in a small volume of EtOAc and treated with TFA (90% TFA/water). After 2h toluene was added and the reaction evaporated and re-evaporated from toluene. The residue was taken up into EtOAc and treated with 2N HCl in diethyl ether. The precipitate was filtered, washed with diethyl ether and dried under vacuum. Crystallisation from ethanol/diethyl ether afforded the title compound (D7) (1.74g). LCMS electrospray (+ve) 252(MH^+).

Description 8

1-Isopropyl-4-(piperidine-4-carbonyl)-[1,4]-diazepane (D8)

Step 1: 1-Benzyl-4-(1-*tert*-butoxycarbonyl-piperidine-4-carbonyl)-[1,4]-diazepane
1-Benzyl-[1,4]-diazepane (3.78g) and 1-*tert*-butoxycarbonyl-piperidine-4-carboxylic acid (5.0g) were dissolved in DCM (150 ml) and TEA (3.6ml) was added followed by HOBT (1.34g) and finally EDC (4.90g). The reaction was stirred at rt overnight. The reaction mixture was then evaporated to a minimum, re-dissolved in DCM (50 ml) and washed with saturated sodium hydrogen carbonate solution (3 x 50ml) and brine (50ml). The organic layer was dried ($MgSO_4$) and evaporated to a crude which was purified by column chromatography [silica gel, step gradient 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM]. Fractions containing pure desired product were combined and evaporated to give the subtitled compound as a pale brown solid (7.1 g).

Step 2: 1-(1-*tert*-Butoxycarbonyl-piperidine-4-carbonyl)-[1,4]-diazepane
The product of D8, Step 1 (7.1g) was dissolved in ethanol (100ml) and 10% palladium on charcoal (1.0g) was added and the reaction hydrogenated for 18h. The catalyst was then removed by filtration and the filtrate evaporated to give the subtitled compound as a clear oil (5.0g).

Step 3: 1-Isopropyl-4-(1-*tert*-butoxycarbonyl-piperidine-4-carbonyl)-[1,4]-diazepane
The product of D8, Step 2 (2.0g) was dissolved in DCM (50 ml) and acetone (0.94ml) added and the mixture stirred for 5min. Sodium triacetoxyborohydride (2.7g) was then added and the reaction stirred at rt for 1.5h. The reaction mixture was then washed with saturated potassium carbonate solution (50 ml), sodium hydrogen carbonate solution (3x 50ml) and brine (50ml). The organic layer was dried ($MgSO_4$) and evaporated to give the subtitled compound as a white solid (1.50 g).

Step 4: 1-Isopropyl-4-(piperidine-4-carbonyl]-[1,4]-diazepane
The product of D8, Step 3 (1.5g) was dissolved in methanol (30ml) and 4N HCl in dioxane (10ml) added. The reaction was stirred at rt for 16h. The reaction mixture was then evaporated to a minimum and the residue basified with saturated potassium carbonate solution (50 ml) and extracted with DCM (3 x 50ml). The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (D8) as a white solid (0.75g). MS electrospray (+ve) 254 (MH^+).

Description 9

1-Isopropyl-4-[1-(4-carboxy-phenyl)-piperidin-4-carbonyl]-piperazine hydrochloride (D9)

Step 1: 1-Isopropyl-4-[1-(4-ethoxycarbonyl-phenyl)-piperidin-4-carbonyl]-piperazine

1-Isopropyl-4-(4-piperidine-4-carbonyl)piperazine (D1) (2.5g), ethyl 4-fluorobenzoate (1.39g) and potassium carbonate (3.55g) was stirred in DMSO (50ml) and heated to 120°C for 2h. The reaction was then heated to 140°C for a further 2h. The reaction was then evaporated to a minimum and the residue re-dissolved in DCM (50ml) and washed with sodium hydrogen carbonate (3 x 50ml) and brine (50ml). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography [silica gel, step gradient 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM]. Fractions containing the required product were evaporated to give the subtitled compound as a white solid (1.20g). MS electrospray (+ve) 388 (MH^+).

Step 2: 1-Isopropyl-4-[1-(4-carboxy-phenyl)-piperidin-4-carbonyl]-piperazine hydrochloride

The product of D9, Step 1 (1.22g) was dissolved in dioxane (20ml) and 2M lithium hydroxide (3.1ml) added and the mixture heated to reflux for 2h. The reaction mixture was then evaporated to a minimum, re-dissolved in DCM (50ml) and treated with 4N HCl in dioxane (20ml). The mixture was then evaporated (co-evaporated with toluene) to give the title compound (D9) as a white solid (1.51g, contains 2eq. LiCl). MS electrospray (+ve) 360 (MH^+).

Description 10

1-Cyclobutyl-4-(piperidine-4-carbonyl)-[1,4]-diazepane (D10)

Step 1: 1-Cyclobutyl-4-(1-*tert*-butoxycarbonyl-piperidine-4-carbonyl)-[1,4]-diazepane

1-(1-*tert*-Butoxycarbonyl-piperidine-4-carbonyl)-[1,4]-diazepane (2.0 g) (D8, Step 2) was dissolved in DCM (50ml) and cyclobutanone (0.96 ml) added and the mixture stirred for 5min. Sodium triacetoxyborohydride (2.7g) was then added and the reaction stirred at rt for 1.5h. The reaction mixture was then washed with saturated potassium carbonate solution (50ml), sodium hydrogen carbonate solution (3x 50ml) and brine (50ml). The organic layer was dried ($MgSO_4$) and evaporated to give the subtitled compound as a white solid (1.67g).

Step 2: 1-Cyclobutyl-4-(piperidine-4-carbonyl)-[1,4]-diazepane

The product of D10, Step 1 (1.67g) was dissolved in methanol (30ml) and 4N HCl in dioxane (10ml) added. The reaction was then stirred at rt for 16h. The reaction mixture was then evaporated to a minimum and the residue basified with saturated potassium carbonate solution (50ml) and extracted with DCM (3 x 50ml). The organic layer was then dried ($MgSO_4$) and evaporated to give the title compound (D10) as a white solid (1.50g). MS electrospray (+ve) 266 (MH^+). ^1H NMR δ [DMSO-d6]: 3.60 (5H, m), 3.30 (1H, m), 3.10-2.65 (4H, m), 2.41 (4H, m), 2.05-1.58 (12H, m).

Description 11

1-(5-Cyanopyridin-2-yl)-4-piperidinecarboxylic acid (D11)

Step 1: Ethyl 1-(5-cyanopyridin-2-yl)-4-piperidinecarboxylate
Piperidine-4-carboxylic acid ethyl ester (5.7g) was dissolved in DMSO (100ml) and potassium carbonate added followed by 6-chloronicotinitrile (5.0g). The reaction was heated to 50°C for 4h under argon. The reaction mixture was then evaporated to a minimum and the residue acidified to pH-2 with aqueous 1N HCl solution. The aqueous mixture was then extracted with DCM (2 x 50ml). The combined organic layers were then washed with sodium hydrogen carbonate (2 x 50ml), brine (50ml) and then dried ($MgSO_4$) and evaporated to give the subtitled compound as a white solid (8.96g).
Step 2: 1-(5-Cyanopyridin-2-yl)-4-piperidinecarboxylic acid
The product of D11, Step 1 (8.96g) was dissolved in 1,4-dioxane (50ml) and 1M LiOH solution (38ml) added and the solution stirred at rt for 4h. The reaction mixture was then evaporated to a minimum and the residue acidified to pH-2 with aqueous 2N HCl acid and extracted with DCM (2 x 100ml). The combined organic extracts were then washed with brine (50ml), dried ($MgSO_4$) and evaporated to a give the title compound (D11) as a white powder (6.60g).

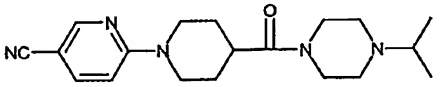
Description 12
1-(5-Cyanopyridin-2-yl)-4-piperidinecarbonyl chloride (D12)
1-(5-Cyanopyridin-2-yl)-4-piperidinecarboxylic acid (D11) (5.5g) was heated to reflux in thionyl chloride (50ml) for 1.5h and then allowed to stand at rt under argon overnight. The reaction was then evaporated (co-evaporated 3 x with DCM) to give the title compound (D12) as a yellow solid (5.70g).

Description 13
(2*R*,6*S*)-4-[1-(4-Cyanophenyl)-piperidine-4-carbonyl]-2,6-dimethylpiperazine hydrochloride (D13)
1-(4-Cyanophenyl)-piperidine-4-carboxylic acid (D3) (6.92g), HOBT (1.77g), TEA (4.7 ml) and (2*R*,6*S*)-2,6-dimethylpiperazine (3.0g) were stirred in DMF (25ml) and then EDC (3.7g) was added and the reaction stirred at rt overnight. The solvent was evaporated and the residue redissolved in DCM (100ml) and washed with saturated sodium hydrogen carbonate (2 x 80ml), brine (75ml) and the organic layer dried ($MgSO_4$) and evaporated. The crude product was then purified by column chromatography [silica gel, step gradient 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM]. Fractions containing the required product were evaporated to give the free base compound which was dissolved in DCM (10ml) and treated with 1N HCl in diethyl ether to give the subtitled compound as a white precipitate which was filtered off (1.80g). MS electrospray (+ve) 327 (MH^+).

Description 14
1-[1-(5-Cyanopyridin-2-yl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (D14)

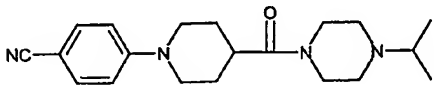
1-*tert*-Butoxy-carbonyl-[1,4]-diazepane (4.0g) and TEA (3.63ml) were stirred in DCM (15 ml). 1-(5-Cyanopyridin-2-yl)-4-piperidinecarbonyl chloride (D12) (5.70g) in DCM (15ml) was then added and the reaction stirred at rt under argon overnight. The reaction mixture was then washed with sodium hydrogen carbonate (2 x 50ml) and brine (50ml). The organic layer was dried ($MgSO_4$) and evaporated to give a crude product which was purified by column chromatography [silica gel, gradient elution 0-100% EtOAc in hexane]. Pure product fractions were combined and evaporated to give a pale yellow solid (1.10g) which was dissolved in 1,4-dioxane (30ml) treated with 4N HCl in 1,4-dioxane (5ml) and then stirred at rt for 2h. The solvent was evaporated to give the title compound (D14) as a yellow solid (0.92g).

Example 1
1-Isopropyl-4-[1-(5-cyano-pyridin-2-yl)-piperidine-4-carbonyl]-piperazine hydrochloride (E1)



To 1-isopropyl-4-(piperidine-4-carbonyl)-piperazine (0.239g) (D1) and 2-chloro-5-cyano-pyridine (0.138g), dissolved in DMSO (5ml), was added potassium carbonate (0.14g). The reaction was heated to 80°C for 4h before cooling and dilution with saturated sodium hydrogen carbonate (50ml) and EtOAc (80ml). The EtOAc layer was washed further with brine (3x80ml) and then extracted with 1N HCl. The aqueous HCl extract was basified and back-extracted with EtOAc which was concentrated under vacuum. A solution of 2N HCl in diethyl ether (1ml) was then added and the precipitate filtered and washed with diethyl ether. Crystallisation from methanol afforded the title compound (E1) (0.15g). ^{1}H NMR δ [DMSO-d6]:1.29 (6H, d, J= 6.4Hz), 1.4-1.6 (2H, m), 1.7-1.85 (2H, m), 2.8-3.27 (6H, m), 3.32-3.52 (3H, m), 3.69 (1H, m), 4.24 (1H, brd, J=13Hz), 4.35-4.55 (3H, m), 6.96 (1H, d, J=9.1Hz), 7.84 (1H, dd, J=9.1Hz and 1.5Hz), 8.47 (1H, d, J=1.5Hz) and 11.36 (1H, brs). MS electrospray; (+ve ion) 342 (MH+).

Example 2
1-Isopropyl-4-[1-(4-cyanophenyl)-piperidine-4-carbonyl]-piperazine hydrochloride (E2)

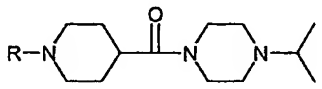


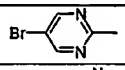
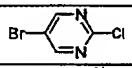
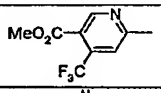
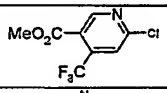
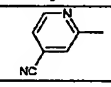
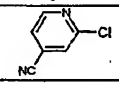
The title compound (E2) was prepared from 4-fluorobenzonitrile and 1-isopropyl-4-(piperidine-4-carbonyl)-piperazine (D1) according to the procedure described in Example 1, except that the reaction was carried out at 120°C for 8h. ^{1}H NMR δ [DMSO-d6]: 1.29 (6H, d, J= 6.5 Hz), 1.4-1.8 (4H, m), 2.8-3.1 (5H, m), 3.11-3.22 (1H, m), 3.31-3.5 (3H, m),

3.62-3.77 (1H, m), 3.89-4 (2H, m), 4.2 (1H, brd, J=13.5Hz), 7.03 (2H, d, J=9Hz), 7.56 (2H, d, J=9Hz) and 11.43 (1H, brs). MS electrospray; (+ve ion) 341 (MH+).

Examples 3-5 (E3-E5)

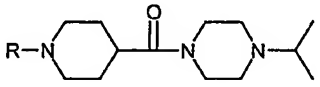
Examples 3 - 5 were prepared from 1-isopropyl-4-(piperidine-4-carbonyl)-piperazine (D1) and the appropriate heteroaryl chloride using the procedure described in Example 1 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.

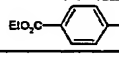
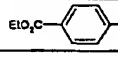


Example No	R	Heteroaryl Chloride	Mass Spectrum (ES^+)
E3			$[MH]^+$ 396/398
E4			$[MH]^+$ 443
E5			$[MH]^+$ 342

Examples 6-8 (E6-E8)

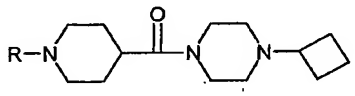
Examples 6 - 8 were prepared from 1-isopropyl-4-(piperidine-4-carbonyl)-piperazine (D1) and the appropriate aryl fluoride using the procedure described in Example 2 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.

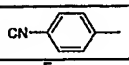
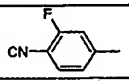
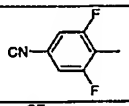
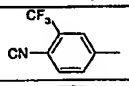
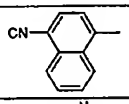
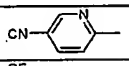
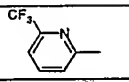
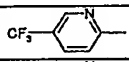
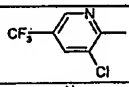
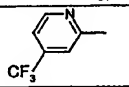
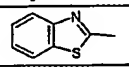


Example No	R	Aryl Fluoride	Mass Spectrum (ES^+)
E6			$[MH]^+$ 341
E7			$[MH]^+$ 341
E8			$[MH]^+$ 388

Examples 9-19 (E9-E19)

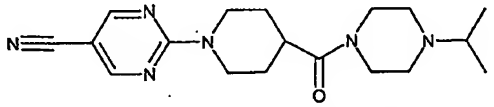
Examples 9 - 19 were prepared from 1-cyclobutyl-4-(piperidine-4-carbonyl)-piperazine di-hydrochloride (D7) and the appropriate aryl halide, using the procedures described in Example 1 (for E14-E19) and Example 2 (for E9-E13), and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R	Mass Spectrum (ES^+)
E9		$[MH]^+$ 353
E10		$[MH]^+$ 371
E11		$[MH]^+$ 389
E12		$[MH]^+$ 421
E13		$[MH]^+$ 403
E14		$[MH]^+$ 354
E15		$[MH]^+$ 397
E16		$[MH]^+$ 397
E17		$[MH]^+$ 431
E18		$[MH]^+$ 397
E19		$[MH]^+$ 385

Example 20

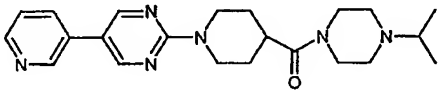
1-Isopropyl-4-[1-(5-cyano-pyrimidin-2-yl)-piperidine-4-carbonyl]-piperazine hydrochloride (E20)



1-Isopropyl-4-[1-(5-bromo-pyrimidin-2-yl)-piperidine-4-carbonyl]-piperazine (D2) (0.5g) in DMF (10ml) was treated with CuCN (0.1g) and the reaction mixture was refluxed overnight. The DMF was removed by evaporation and the residue was partitioned

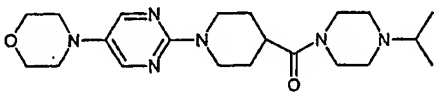
between H_2O/EtOAc (20:20ml). The EtOAc layer was dried ($MgSO_4$) and evaporated to dryness and purified first by chromatography [silica gel 0-10% MeOH (containing 10% 0.88 ammonia solution)/ DCM] followed by further purification on a Waters Mass Directed Auto Preparative HPLC eluting with (0.1% formic acid in water and 0.1% formic acid acetonitrile gradient 10-100%). The isolated product peaks were combined and evaporated to give the desired product as the formate salt which was converted to the HCl salt in MeOH/ethereal 1N HCl (2ml). The solvents were removed by evaporation to give the title compound (E20) as a white solid (17mg).^{1}H NMR δ [DMSO-d6]: 1.29 (6H, d, J=6.5), 1.40-1.58 (2H, m),1.70-1.81 (2H, m), 2.90-3.5 (10H, m), 4.25-4.8 (4H, m), 8.74 (2H, s),10.9 (1H, bs). LCMS electrospray (+ve) 343 (MH^+).

Example 21
1-Isopropyl-4-{1-[5-(pyridin-3-yl)-pyrimidin-2-yl]-piperidine-4-carbonyl}-piperazine hydrochloride (E21)



A mixture of 1-isopropyl-4-[1-(5-bromo-pyrimidin-2-yl)-piperidine-4-carbonyl]-piperazine (D2) (0.25g), 3-pyridyl boronic acid (0.1g), 2M K_2CO_3 (1.5ml) and EtOH (1.5ml) in toluene (10ml) were stirred under a stream of argon for 30min. After this time $Pd(PPh_3)_4$ (50mg) was added and the reaction mixture was refluxed overnight. Water (1ml) was added and the reaction mixture was stirred at rt for 5min. The mixture was passed through a 20g Varian Hydromatrix disposable liquid/liquid extraction cartridge and washed with EtOAc (30ml). The EtOAc layer was absorbed on silica (4g) and purified by chromatography [silica gel 0-10% MeOH (containing 10% 0.88 ammonia solution)/ DCM]. The free base was dissolved in MeOH (5ml) and treated with 1N ethereal HCl (2ml). The solvents were removed by evaporation to give the title compound (E21) as a white solid (150mg).^{1}H NMR δ [DMSO-d6]: 1.29 (6H, d, J=6.5), 1.4-1.6 (2H, m),1.7-1.8 (2H, m), 2.8-2.9 (1H, m),3.0-3.2 (6H, m),3.38-3.44 (2H, m), 3.42-3.5 (1H, m), 3.66-3.73 (1H, m), 4.25-4.3 (1H, s), 4.47-4.5 (1H, m) ,4.7-4.8 (2H, m), 8.0-8.08 (1H, m), 8.78-8.81 (2H, dd, J=2.5), 8.90 (1H, s), 9.23 (1H, d, J=1.5), 11.20 (1H, brs); LCMS electrospray (+ve) 395(MH^+).

Example 22
1-Isopropyl-4-[1-(5-morpholino-pyrimidin-2-yl)-piperidine-4-carbonyl]-piperazine hydrochloride (E22)

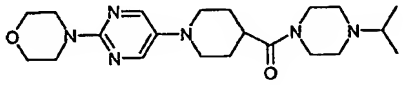


Bis(tri-t-butylphosphine)palladium(0) (20mg) was added to o-xylene(10ml) and the reaction mixture was stirred at rt for 10min to give an orange coloured solution. 1-Isopropyl-4-[1-(5-bromo-pyrimidin-2-yl)-piperidine-4-carbonyl]-piperazine (D2) (0.25g) in o-xylene (10ml) was added to the orange solution followed by addition of NaO^tBu (84mg)

and morpholine (0.12g) The reaction mixture was refluxed for 1h. After cooling the reaction mixture was partitioned between H_2O/EtOAc (30:20ml), the EtOAc layer was dried($MgSO_4$) and filtered, the filtrate was absorbed onto silica gel (3g) and purified by chromatography [silica gel 0-10% MeOH (containing 10% 0.88 ammonia solution)/ DCM]. The free base was taken up in dry MeOH (3ml) and treated with ethereal HCl. The solvents were removed by evaporation to give the title compound (E22) as a white solid (67mg).^{1}H NMR δ [DMSO-d6]: 1.29 (6H, d, J=6.5), 1.4-1.6 (2H, m),1.68-1.7 (2H, m), 2.92-3.16 (10H, m),3.37-3.65 (4H, m),3.74-3.76 (4H, m),4.22-4.25(1H, m), 4.47-4.60(3H, m), 8.26 (2H, s),10.85 (1H, bs). LCMS electrospray (+ve) 403 (MH^+).

Example 23

1-Isopropyl-4-[1-(2-morpholino-pyrimidin-5-yl)-piperidine-4-carbonyl]-piperazine hydrochloride (E23)



Step 1: 4-(5-Bromo-pyrimidin-2-yl)-morpholine

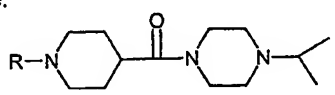
Potassium carbonate (0.34g) was added to a solution of 2-chloro-5-bromo-pyrimidine (0.5g) in DMF (20ml). The reaction mixture was stirred at rt for 15min. Morpholine (0.2g) was added and the reaction mixture was stirred at rt for 2h. The excess DMF was removed by evaporation and the residue was partitioned between H_2O/EtOAc (30:30ml) The EtOAc layer was dried ($MgSO_4$) and evaporated to dryness to give the sub-title compound as a cream solid (0.2g). LCMS electrospray(+ve) 246 (MH^+).

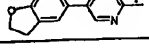
Step 2: 1-Isopropyl-4-(2-morpholino-pyrimidin-5-yl)-piperidine-4-carbonyl)-piperazine hydrochloride

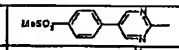
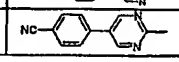
The title compound was prepared by reacting the product of E23, Step 1 with 1-isopropyl-4-(piperidine-4-carbonyl)-piperazine (D1) using the conditions described in Example 22 . ^{1}H NMR δ [DMSO-d6]; 1.29 (6H, d, J=6.5), 1.78 (4H,m), 2.80-3.1 (4H,m),3.2-4.7 (18H,m), 8.35 (2H, s),10.65 (m, 1H). LCMS electrospray(+ve) 403 (MH^+).

Examples 24-26 (E24-E26)

Examples 24 - 26 were prepared from 1-isopropyl-4-[1-(5-bromo-pyrimidin-2-yl)-piperidine-4-carbonyl]-piperazine (D2) and an appropriate aryl boronic acid using the procedure described in Example 21 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.

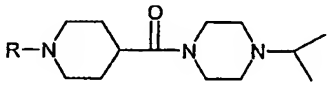


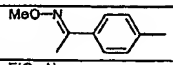
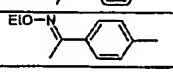
Example No	R	Mass Spectrum (ES^+)
E24		$[MH]^+$ 436

E25		$[MH]^+$ 472
E26		$[MH]^+$ 419

Examples 27 and 28 (E27-E28)

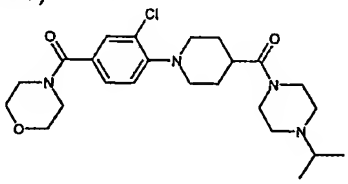
Examples 27 - 28 were prepared and isolated as for Example 1, from 1-isopropyl-4-(piperidine-4-carbonyl)-piperazine (D1) (0.239g) and 4-fluoro-acetophenone at 120°C for 2h, followed by condensation of the product with the corresponding hydroxylamine hydrochloride in refluxing methanol for 1h. Conversion to the HCl salts, by precipitation from ethyl acetate with 2N HCl in diethyl ether, and crystallisation from ethanol afforded the examples which displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R	Mass Spectrum (ES^+)
E27		$[MH]^+$ 387
E28		$[MH]^+$ 401

Example 29

1-Isopropyl-4-{1-[2-chloro-4-(morpholino-carbonyl)-phenyl]-piperidine-4-carbonyl}-piperazine hydrochloride (E29)



Step 1: 1-Isopropyl-4-[1-(2-chloro-4-chlorocarbonyl-phenyl)-piperidin-4-carbonyl]-piperazine hydrochloride

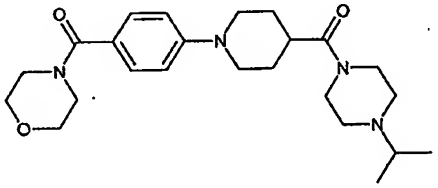
1-Isopropyl-4-[1-(4-carboxy-phenyl)-piperidin-4-carbonyl]-piperazine hydrochloride (D9) (0.25g) was dissolved in thionyl chloride (10ml) and heated at reflux for 1.5h. The reaction mixture was then evaporated to a minimum (co-evaporated with DCM, 3 x 10ml) to give the subtitled compound as a yellow oil (0.25g).

Step 2: 1-Isopropyl-4-{1-[2-chloro-4-(morpholino-carbonyl)-phenyl]-piperidine-4-carbonyl}-piperazine hydrochloride

A stirred mixture of the product of E29, Step 1 (0.25 g) and diethylaminomethyl polystyrene (3.2 mmol/g, 0.45 g) in DCM (10ml) at rt was treated with morpholine (0.035 g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM]. Fractions containing the required product were evaporated, redissolved in DCM, treated

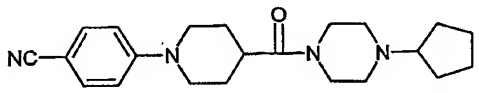
with excess hydrogen chloride (1M solution in diethyl ether) and then concentrated and the residue crystallised from acetone to yield the title compound (E29) as a white powder (0.018 g). MS electrospray (+ion) 464 (MH^+). ^1H NMR δ [DMSO-d6]: 10.30 (1H, s), 7.45 (1H, s), 7.32 (1H, d, J=8.0Hz), 7.17 (1H, d, J=8.4Hz), 4.55 (1H, m), 4.20 (1H, m), 3.62-3.28 (15H, m), 3.15-2.67 (5H, m), 1.77 (4H, m), 1.28 (6H, d, J=6.4Hz).

Example 30
1-Isopropyl-4-{1-[4-(morpholino-carbonyl)-phenyl]-piperidine-4-carbonyl}-piperazine hydrochloride (E30)



To a stirred solution of 1-isopropyl-4-[1-(4-carboxy-phenyl)-piperidin-4-carbonyl]-piperazine hydrochloride (D9) (0.25g), morpholine (0.035ml), HOBT (0.03g), TEA (0.16 ml) in DCM (10 ml) was added EDC (0.10g). DMF (2ml) was added and the reaction stirred under argon overnight. The reaction mixture was then evaporated to a minimum and residue dissolved in DCM (50ml) and washed with sodium hydrogen carbonate (3 x 50 ml) and then brine (50ml). The organic layer was then dried ($MgSO_4$) and evaporated to give the free base product. Free base was converted to the HCl salt by dissolving in DCM (5ml) and treating with excess 1 HCl in diethyl ether, evaporated and then crystallised from acetone to give the title compound (E30) as a white solid (0.03g). MS electrospray (+ve) 429 (MH^+). ^1H NMR δ [DMSO-d6]: 10.85 (1H, s), 7.38 (2H, d, J=8.4Hz), 7.08 (2H, m), 4.51 (1H, m), 4.22 (1H, m), 3.81 (2H, m), 3.68-3.35 (12H, m), 3.20-2.81 (6H, m), 1.74 (4H, m), 1.29 (6H, d, J=6.4Hz).

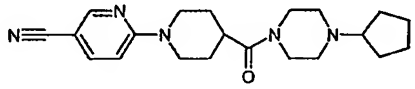
Example 31
1-Cyclopentyl-4-[1-(4-cyano-phenyl)-piperidine-4-carbonyl]-piperazine hydrochloride (E31)



Potassium carbonate (0.8g) was added to a stirred solution of 1-cyclopentyl-4-(piperidine-4-carbonyl)-piperazine di-hydrochloride (D5) (0.5g) in dry DMSO (15ml) followed by the addition of 4-benzonitrile (0.35g). The reaction mixture was heated at 140°C for 2h. After cooling the reaction mixture was partitioned between H_2O/EtOAc (30:30ml). The EtOAc layer was dried ($MgSO_4$) filtered and the filtrate was absorbed onto silica gel (4g) and purified by chromatography [silica gel 0-10% MeOH (containing 10% 0.88 ammonia solution)/ DCM]. The free base was dissolved in MeOH (3ml) and treated with 1N ethereal HCl (2ml). The solvents were removed by evaporation to give

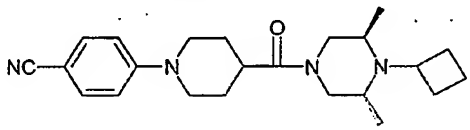
the title compound (E31) as a white solid (63mg).^{1}H NMR δ [DMSO-d6]; 1.5-1.9 (12H, m), 2.9-3.06 (4H, m) 3.9-3.96 (2H, m), 4.18-4.45 (2H, m), 7.01 (2H, d J=9.2), 7.55 (2H,d J=9.2), 11.28 (1H, brs). LCMS electrospray(+ve) 356 (MH^+).

Example 32
1-Cyclopentyl-4-[1-(5-cyano-pyrid-2-yl)-piperidine-4-carbonyl]-piperazine hydrochloride (E32)



The title compound (E32) was prepared from 2-chloro-5-cyano-pyridine and 1-cyclopentyl-4-(piperidine-4-carbonyl)-piperazine di-hydrochloride (D5) according to the procedure described in Example 31. ^{1}H NMR δ [DMSO-d6]: 1.5 (4H, m), 1.67-1.88 (6H, m),1.98-2.02 (2H, m), 2.87-2.97 (6H, m), 3.4-3.7 (4H, m), 4.17-4.7 (4H, m) 6.94 (1H, d, J=9Hz), 7.8 (1H, d, J=9Hz), 8.4 (1H, s) 11.5 (1H, brs). LCMS electrospray (+ve) 368 (MH+).

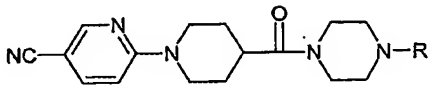
Example 33
(2*R*,6*S*)-1-Cyclobutyl-4-[1-(4-cyanophenyl)-piperidine-4-carbonyl]-2,6-dimethylpiperazine hydrochloride (E33)



(2*R*,6*S*)-4-[1-(4-Cyanophenyl)-piperidine-4-carbonyl]-2,6-dimethylpiperazine hydrochloride (D13) (0.30g), TEA (0.4ml), cyclobutanone (0.13g) and sodium triacetoxyborohydride (0.40g) in DCM (5ml) were heated to 100°C in a microwave reactor for 5min. The reaction mixture was then washed with saturated potassium carbonate solution (2 x 30ml), and brine (30ml). The organic layer was then dried ($MgSO_4$) and evaporated give the crude product which was purified by column chromatography [silica gel, step gradient 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM]. Fractions containing the required product were evaporated to give the free base compound which was converted to the HCl salt by redissolving in DCM and then treating with excess hydrogen chloride (1M solution in diethyl ether), evaporating and then crystallising from acetone to give the title compound (E33) as a pale grey solid (0.053g). MS electrospray (+ve) 381 (MH^+). ^{1}H NMR δ [DMSO-d6]: 11.28 plus 10.10 (1H, m, rotomers), 7.59 (2H, d, J=8.4 Hz), 7.00 (2H, d, J=8.0Hz), 4.31-3.73 (6H, m), 3.60-3.22 (3H, m), 2.97 (3H, m), 2.50-2.08 (4H, m), 1.78-1.61 (6H, m), 1.50 -1.10 (6H, m).

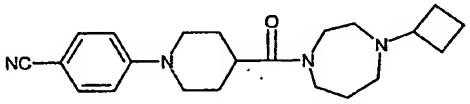
Examples 34 and 35 (E34 and E35)

Examples 34 - 35 were prepared as for Example 1, from N-cyclopentyl-piperazine and N-isopentyl-piperazine respectively, and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



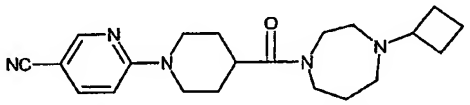
Example No	R	Mass Spectrum (ES^+)
E34		$[MH]^+$ 368
E35		$[MH]^+$ 370

Example 36
1-Cyclobutyl-4-[1-(4-cyanophenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E36)



1-[1-(4-Cyanophenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (D4) (0.30g) was dissolved in DCM (10ml). TEA (0.4 ml) and cyclobutanone (0.14ml) were added and stirred for 5 min. Sodium triacetoxyborohydride (0.40g) was then added and the reaction stirred at rt overnight. The reaction was then washed with aqueous saturated potassium carbonate solution (2 x 30ml), brine (30ml), dried ($MgSO_4$) and evaporated. The free base was redissolved in DCM and treated with excess hydrogen chloride (1M solution in diethyl ether) and concentrated to yield the title compound (E36) as a white solid (0.16g). MS electrospray (+ve) 367 (MH^+). ^{1}H NMR δ [DMSO-d6]: 10.95-10.78 (1H, m), 7.56 (2H, d, J=9.2Hz), 7.02 (2H, d, J=8.8Hz), 4.20-3.95 (3H, m), 3.62-3.39 (5H m), 3.07 (1H, m), 2.98-2.70 (5H, m), 2.49-2.01 (6H, m), 1.72-1.57 (6H, m).

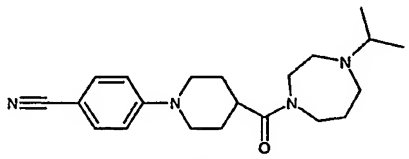
Example 37
1-Cyclobutyl-4-[1-(5-cyanopyridin-2-yl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E37)



1-[1-(5-Cyanopyridin-2-yl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (D14) (0.30g) was dissolved in DCM (10ml) and TEA (0.4ml) was added followed by cyclobutanone (0.14ml). The reaction was stirred for 5min under argon and then sodium triacetoxyborohydride (0.41g) was added and the reaction stirred at rt for 4h. The reaction mixture was washed with saturated aqueous potassium carbonate (2 x 30ml), saturated sodium hydrogen carbonate (2 x 50ml) and brine (50ml). The organic layer

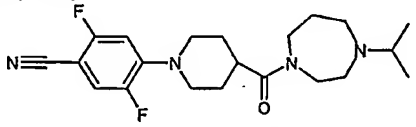
was then dried ($MgSO_4$) and evaporated to a crude which was purified by column chromatography [silica gel, step gradient 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM] to give the free base product which was converted to the HCl salt by redissolving in DCM and then treating with excess hydrogen chloride (1M solution in diethyl ether) and concentrating to yield the title compound (E37) as a pale yellow solid (0.047g). MS electrospray (+ve) 368 (MH^+). ^1H NMR δ [DMSO-d6]: 10.80-10.50 (1H, m), 8.47 (1H, s), 7.83 (1H, d, J=8.8Hz), 6.95 (2H, d, J=8.8Hz), 4.44 (2H, m), 4.05 (1H, m), 3.85-3.28 (6H, m), 3.07-2.72 (5H, m), 2.41-2.01 (6H, m), 1.82-1.41 (6H, m).

Example 38
1-Isopropyl-4-[1-(4-cyanophenyl)-piperidine-4-carbonyl]-[1,4]-diazepane-hydrochloride (E38)



Triethylamine (0.18ml) was added to a solution of 1-[1-(4-cyanophenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (D4) (0.3g) in dry DCM (15ml) followed by the addition of acetone (0.15g). The reaction was stirred at rt for 30min followed by the addition of sodium triacetoxyborohydride (0.4g). After 18h 1N NaOH (2ml) was added and stirring continued for a further 15min. The reaction was then washed with water and the DCM layer was separated, dried ($MgSO_4$), absorbed onto silica gel (4g) and purified by chromatography [silica gel 0-10% MeOH (containing 10% 0.88 ammonia solution)/ DCM]. The free base was dissolved in MeOH (3ml) and treated with 1N ethereal HCl (2ml). The solvent was removed by evaporation to give the title compound (E38) as a white solid (0.1g).^1H NMR δ [DMSO-d6]; 1.27 (6H, d J=6.5Hz), 1.58 (2H, m), 1.74 (2H, m), 2.08 (1H, m), 2.32 (1H, m), 2.75-3.25 (6H, m), 3.35-3.76 (6H, m), 3.9-4.08 (2H, m), 7.0 (2H,d, J=8.8), 7.54 (2H, d J=8.8), 10.38-10.58 (1H, m). LCMS electrospray (+ve) 355 (MH^+).

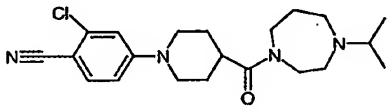
Example 39
1-Isopropyl-4-[1-(4-cyano-2,5-difluorophenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E39)



K_2CO_3 (0.5g) was added to a solution of 1-isopropyl-4-(piperidine-4-carbonyl]-[1,4]-diazepane (D8) (0.2g) in dry DMSO (2ml), and the resulting mixture was stirred at rt for 15min, followed by the addition of 2,4,5-trifluorobenzonitrile (0.24g) in dry DMF (1ml). The reaction was then heated at 140°C for 2h before cooling to rt. Excess potassium carbonate was removed by filtration and the crude reaction mixture was purified first by

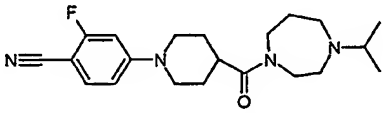
adding the crude reaction to a Varian 10g SCX column and eluting with MeOH (40ml), then eluting with 10% 0.88 ammonia solution in MeOH (20ml) which was evaporated to afford a residue that was further purified using a Waters mass directed auto preparative HPLC. The purified fractions were combined and the aqueous solvents were removed by evaporation and the residue re-dissolved in MeOH (2ml) and treated with 1N ethereal HCl (1ml) which gave a white solid which was washed with diethyl ether to give the title compound (E39) (34mg).^{1}H NMR δ [MeOH-d4]; 1.37 (6H, m),1.87 (4H, m), 2.19-2.29 (2H, m), 2.94-3.00 (3H, m), 3.29-3.3 (2H, m), 3.53-3.58 (7H, m), 3.86-3.98 (1H, m), 4.04-4.1 (1H, m), 6.9 (1H, dd, J=11.6Hz), 7.4 (1H, dd, J=12.4hZ). LCMS electrospray (+ve) 391 (MH^+).

Example 40
1-Isopropyl-4-[1-(4-cyano-3-chlorophenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E40)



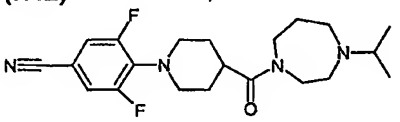
The title compound (E40) was prepared using 2-chloro-4-fluorobenzonitrile and the procedure described in Example 39. ^{1}H NMR δ [MeOH-d4]; 1.37 (6H, m),1.78-1.9 (4H, m), 2.29 (2H, m), 2.99-3.00 (3H, m), 3.04-3.31 (2H, m), 3.47-3.58 (5H, m), 3.87 (1H, m), 3.97-4.07 (2H, m), 4.07-4.09 (1H), 6.96 (1H, d, J=8.8Hz), 7.08 (1H, d, J=2Hz), 7.51 (1H, J=8.8Hz). LCMS electrospray (+ve) 389 (MH^+).

Example 41
1-Isopropyl-4-[1-(4-cyano-3-fluoro-phenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E41)



The title compound (E41) was prepared using 2,4-difluorobenzonitrile and the procedure described in Example 39. ^{1}H NMR δ [MeOH-d4]: 1.37 (6H, m),1.9 (4H, m), 2.19-2.33 (2H, m), 2.89-2.98 (3H, m), 3.27-3.3 (2H, m), 3.5-3.78 (6H, m), 3.80-3.90 (1H, m), 4.07-4.15 (1H, m), 4.07-4.09 (1H), 7.15 (1H, t, J=8.4Hz), 7.44 (2H, dd J=6.4Hz). LCMS electrospray (+ve) 373 (MH^+).

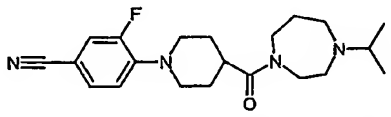
Example 42
1-Isopropyl-4-[1-(4-cyano-2,6-difluoro-phenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E42)



The title compound (E42) was prepared using 3,4,5-trifluorobenzonitrile and the procedure described in Example 39. ^{1}H NMR δ [MeOH-d4]: 1.37 (6H, m), 1.78-1.92 (4H, m), 2.15-2.38 (2H, m), 2.80-2.93 (1H, m), 3.17-3.27 (4H, m), 3.4-3.78 (7H, m), 3.80-3.90 (1H, m), 4.07-4.15 (1H, m), 7.35 (2H, dd, J= 2.4Hz). LCMS electrospray (+ve) 391 (MH^+)

Example 43

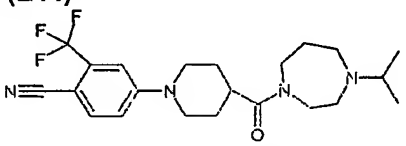
1-Isopropyl-4-[1-(4-cyano-2-fluoro-phenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E43)



The title compound (E43) was prepared using 3,4-difluorobenzonitrile and the procedure described in Example 39. ^{1}H NMR δ [MeOH-d4]: 1.37 (6H, m),1.73-1.89 (4H, m), 2.18-2.37 (2H, m), 2.98-3.08 (3H, m), 3.15-3.27 (2H, m), 3.48-3.78 (5H, m), 3.80-3.90 (1H, m), 3.98-4.12 (2H, m), 4.05-4.12 (1H), 6.7-6.8 (2H, m), 7.45 (1H, t, J=8Hz). LCMS electrospray (+ve) 373 (MH^+).

Example 44

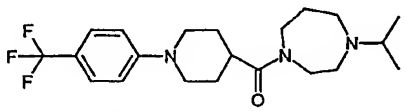
1-Isopropyl-4-[1-(4-cyano-3-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E44)



The title compound (E44) was prepared using 2-trifluoromethyl-4-fluorobenzonitrile and the procedure described in Example 39. ^{1}H NMR δ [MeOH-d4]: 1.38 (6H, m), 1.75-1.91 (4H, m), 2.23-2.37 (2H, m), 2.80-3.08 (4H, m), 3.3-4.08 (10H, m), 7.18 (1H, d, J=8.8Hz), 7.25 (1H, d, J=2.4), 7.68 (1H, d, J=8.8Hz). LCMS electrospray (+ve) 423 (MH^+).

Example 45

1-Isopropyl-4-[1-(4-trifluoromethyl-phenyl)-piperidine-4-carbonyl]-[1,4]-diazepane hydrochloride (E45)

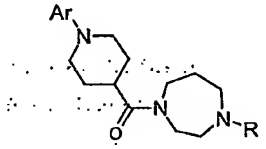


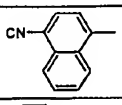
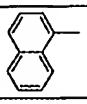
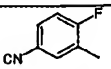
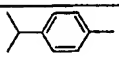
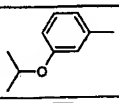
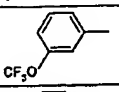
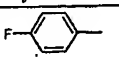
To 4-trifluoromethyl-iodobenzene (0.2g) under argon in dry degassed dioxane (1.5ml) was added bis(dibenzylideneacetone)palladium (0.02g) followed by 2-dicyclohexylphosphine-2'-(N,N-dimethylamino)-biphenyl (0.055g). After 15min this solution was added to 1-isopropyl-4-(piperidine-4-carbonyl]-[1,4]-diazepane (D8) (0.15g) as a slurry in dry degassed dioxane (1.5ml) under argon. This was followed by addition of sodium-t-butoxide (0.06g) and heating to 100^{0}C for 2h. After cooling, saturated ammonium chloride solution (10ml) was added along with EtOAc (20ml). The reaction

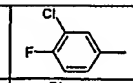
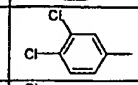
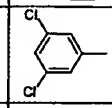
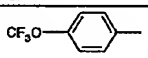
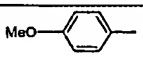
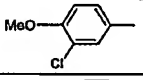
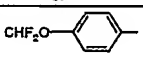
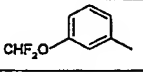
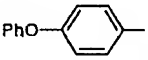
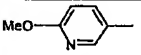
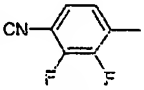
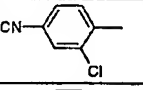
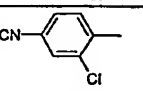
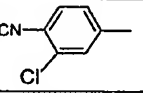
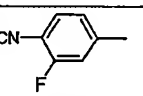
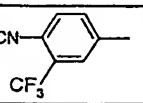
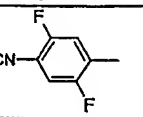
was filtered and washed with brine (2x) before being extracted with 1N HCl and then neutralised with potassium carbonate solution and back extracted into EtOAc. Concentration to low volume and addition of 2N HCl in diethyl ether caused the title hydrochloride salt to precipitate. Decantation of the supernatant and repeated trituration of the residue with diethyl ether afforded crude product that was crystallised from acetonitrile to afford the title compound (E45) (0.078g). ^{1}H NMR δ [MeOH-d4]: 1.38 (6H, m), 2.0-2.34 (6H, m), 2.86-4.11 (14H, m), 7.5-7.6 (2H, m) and 7.71-7.77 (2H, m). LCMS electrospray (+ve) 398 (MH^+).

Examples 46-69 (E46-E69)

Example 46 and Examples 63-69 were prepared from either 1-isopropyl-4-(piperidine-4-carbonyl)-[1,4]-diazepane (D8) or 1-cyclobutyl-4-(piperidine-4-carbonyl)-[1,4]-diazepane (D10) and the appropriate aryl fluoride using the procedure described in Example 39. Examples 47- 62 were prepared by coupling 1-isopropyl-4-(piperidine-4-carbonyl)-[1,4]-diazepane (D8) with the appropriate aryl halide (bromide or iodide) using the conditions described in Example 45. The products displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	Ar	R	Mass Spectrum (ES^+)
E46			$[MH]^+$ 405
E47			$[MH]^+$ 380 $[MNa]^+$ 402
E48			$[MH]^+$ 373 $[MNa]^+$ 395
E49			$[MH]^+$ 372 $[MNa]^+$ 394
E50			$[MH]^+$ 388 $[2MNa]^+$ 797
E51			$[MH]^+$ 414 $[MNa]^+$ 436
E52			$[MH]^+$ 348 $[MNa]^+$ 370

E53			$[MH]^+$ 382/384 $[MNa]^+$ 404/406
E54			$[MH]^+$ 398/400/402 $[MNa]^+$ 420/422
E55			$[MH]^+$ 398/400/402
E56			$[MH]^+$ 414
E57			$[MH]^+$ 360 $[2MNa]^+$ 741
E58			$[MH]^+$ 394/396 $[MNa]^+$ 416/418
E59			$[MH]^+$ 396 $[MNa]^+$ 418
E60			$[MH]^+$ 396 $[MNa]^+$ 418
E61			$[MH]^+$ 422 $[2MNa]^+$ 865
E62			$[MH]^+$ 361 $[MNa]^+$ 383
E63			$[MH]^+$ 391
E64			$[MH]^+$ 389
E65			$[MH]^+$ 401/403
E66			$[MH]^+$ 401/403
E67			$[MH]^+$ 385
E68			$[MH]^+$ 435
E69			$[MH]^+$ 403

Abbreviations

DMSO dimethylsulfoxide

DMF	N,N-dimethylformamide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
HOAT	1-hydroxy-7-azabenzotriazole
h	hour
min	minutes
rt	room temperature
TFA	trifluoroacetic acid

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50µm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500µg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25µg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10µl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/µl or 50µCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80µl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller.

The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

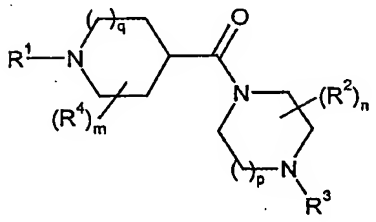
Results

The compounds of Examples E1-E69 were tested in the histamine H3 functional antagonist assay and exhibited pK_b values > 7.5. More particularly, the compounds of E1

E2, E4, E8, E9-E17, E25, E30, E31, E33, E35-E46, E54, E56, E59 and E61-E69 exhibited pK_b values > 8.5. Yet more particularly, the compounds of E36-E38 exhibited pK_b values > 9.0.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:
R^1 represents aryl, heteroaryl, -aryl-X-C_{3-7} cycloalkyl, -heteroaryl-X-C_{3-7} cycloalkyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-heteroaryl, -heteroaryl-X-aryl or –heteroaryl-X-heterocyclyl;
wherein said aryl, heteroaryl and heterocyclyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, -COC_{1-6} alkyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$C(R^{15})$=NOR^{16}, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;
X represents a bond, O, CO, SO_2, OCH_2 or CH_2O;
each R^2 and R^4 independently represents C_{1-4} alkyl;
R^3 represents C_{3-8} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl or -C_{1-4}alkyl-C_{3-6} cycloalkyl;
wherein said C_{3-6} cycloalkyl groups of R^3 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, C_{1-4} alkyl or trifluoromethyl groups;
m and n independently represent 0, 1 or 2;
p and q independently represent 1 or 2;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is a compound of formula E1-E69 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of Alzheimer's disease.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.